

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claims 1-174 (Canceled).

175. (Currently Amended). A method for determining the **Braak** stage of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the disease, which method comprises the steps of:

- (i) introducing into the subject a ligand ~~capable of labelling~~ **that labels** aggregated paired helical filament (PHF) tau protein,
wherein the ligand is capable of crossing the blood brain barrier, and
wherein the ligand is conjugated, chelated, or otherwise associated, with a detectable chemical group,
- (ii) determining the presence and/or amount of ligand bound to extracellular aggregated PHF tau in the medial temporal lobe of the brain of the subject, **and**
- (iii) correlating the result of the determination made in (ii) with the extent of neurofibrillary degeneration in the subject.

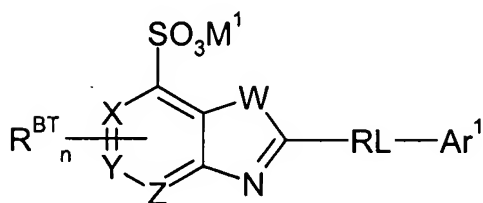
176. (Previously Presented). A method as claimed in claim 175 for use in the diagnosis or prognosis of a tauopathy in a subject believed to suffer from said disease.

177. (Previously Presented). A method as claimed in claim 176 wherein the tauopathy is Alzheimer Disease (AD).

178. (Currently Amended). A method as claimed in claim 175 wherein the extent of neurofibrillary degeneration is related to the **Braak** neuropathological staging of the progression of AD ~~according to the defined hierarchical system shown in Figure 2e.~~

179. (Currently Amended). A method as claimed in claim 175 wherein the ligand is labelled for SPECT and is not ~~capable of being taken up~~ **absorbed** intracellularly or the ligand is labelled for positron emission tomography (PET).

180. (Withdrawn). A method as claimed in claim 175 wherein the ligand is a compound of the formula:



wherein:

W is S, O, or NH;

exactly one of X, Y, and Z is CH or N;

the others of X, Y, and Z are CH;

M^1 is an alkali metal cation selected from: Li, Na, K, or Cs.

RL is a rigid linker group;

Ar^1 is an C_{5-20} aryl group;

n is an integer from 0 to 3; and,

each R^{BT} is independently a core substituent selected from: C1-4 alkyl, hydroxy, C1-4 alkoxy, nitro, cyano, halo, or amino.

181. (Withdrawn). A method as claimed in claim 180 wherein the twist is no greater than that of the compound of Figure 16.

182. (Withdrawn). A method as claimed in claim 180 wherein n is 1, and R^{BT} is independently -Me, -Et, -nPr, or -iPr.

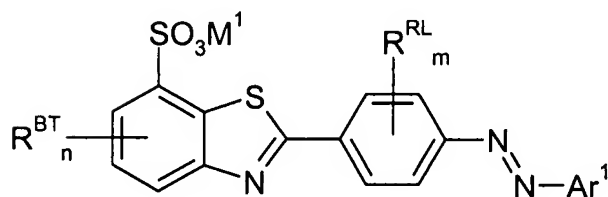
183. (Withdrawn). A method as claimed in claim 180 wherein RL is a group of the formula:

wherein:

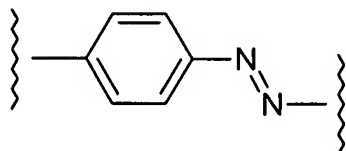
m is an integer from 0 to 4, and

each R^{RL} is independently a rigid linker aryl substituent,

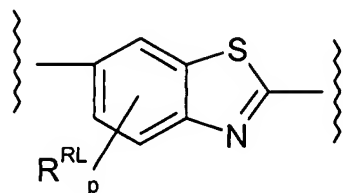
and the ligand has the formula:



184. (Withdrawn). A method as claimed in claim 183 wherein RL is a group of the formula:



185. (Withdrawn). A method as claimed in claim 183 wherein RL is a group of the formula:

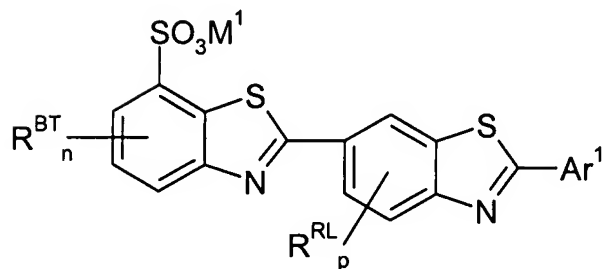


wherein

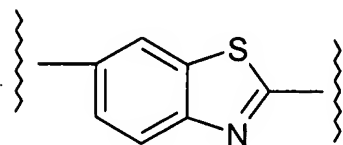
p is an integer from 0 to 3, and

each R^{RL} is independently a rigid linker aryl substituent,

and the compounds have the formula:



186. (Withdrawn). A method as claimed in claim 185 wherein RL is a group of the formula:



187. (Withdrawn). A method as claimed in claim 180 wherein Ar^1 is selected from:

groups derived from benzene (C₆), naphthalene (C₁₀), anthracene (C₁₄), phenanthrene (C₁₄), naphthacene (C₁₈), and pyrene (C₁₆), and

C₅heteroaryl groups derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, and oxatriazole; and

C₆heteroaryl groups derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine), pyrazine (1,4-diazine), triazine, tetrazole, and oxadiazole (furazan), and

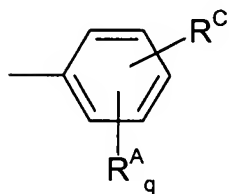
C₉heterocyclic groups derived from benzofuran, isobenzofuran, indole, isoindole, purine, benzimidazole;

C₁₀heterocyclic groups derived from quinoline, isoquinoline, benzodiazine, pyridopyridine, quinoxaline;

C₁₃heterocyclic groups derived from carbazole; and,

C₁₄heterocyclic groups derived from acridine, xanthene, phenoxathiin, phenazine, phenoxazine, phenothiazine.

188. (Withdrawn). A method as claimed in claim 187 wherein Ar¹ is an aryl' group having a phenyl core, and has the formula:



wherein

q is an integer from 0 to 5; and

each R^A is independently an aryl substituent;

wherein each R^A is independently selected from:

-OH, -NH₂, -NHR¹, -NR¹R², -SO₃M², and C₁₋₄ alkyl;

wherein:

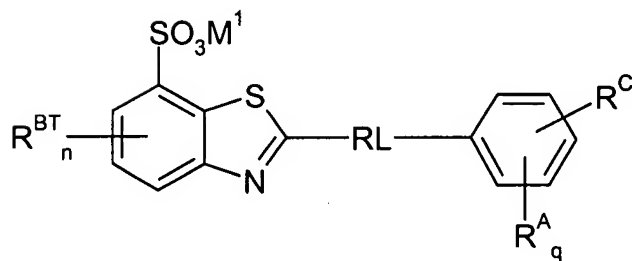
R¹ and R² are each C₁₋₄ alkyl, and

M² is an alkali metal cation selected from Li, Na, K, or Cs

R^C, if present, is a reactive conjugating substituent, or

R^C is, or contains, a detectable label;

and the compound has the formula:



189. (Withdrawn). A method as claimed in claim 188 wherein R^C is present and is a reactive conjugating substituent, and is, or contains,

a reactive functional group suitable for conjugation to another molecule by

chemical reaction therewith, to form a covalent linkage therebetween, or

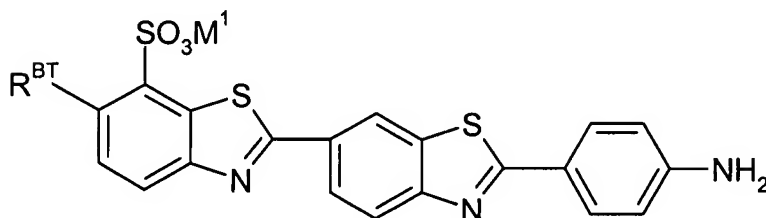
a moiety suitable for conjugation to another molecule by a strong non-covalent interaction, or

a moiety suitable for conjugation to another molecule by complex or chelate formation.

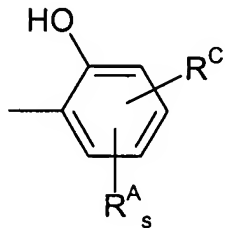
190. (Withdrawn). A method as claimed in claim 189 wherein R^C is present and is, or contains, a technetium-chelating group.

191. (Withdrawn). A method as claimed in claim 188 wherein R^C is present and is, or contains, a detectable label selected from: a dye, a fluorescent marker, an antigenic group, a stable or an unstable isotope, or a positron-emitting carbon atom.

192. (Withdrawn). A method as claimed in claim 186 wherein the ligand has the formula:



193. (Withdrawn). A method as claimed in claim 188 wherein Ar^1 is an aryl group having a hydroxy-substituted phenyl core, and has the formula:



wherein

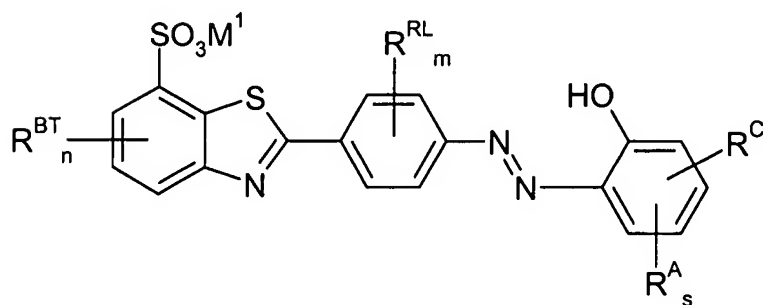
s is an integer from 0 to 4, and

each R^A is independently an aryl substituent, and

R^C , if present, is a reactive conjugating substituent, or

R^C is, or contains, a detectable label.

194. (Withdrawn). A method as claimed in claim 193



wherein:

M^1 is an alkali metal cation selected from Li, Na, K, or Cs;

n is an integer from 0 to 3;

each R^{BT} is a independently benzothiazole substituent;

m is an integer from 0 to 4;

each R^{RL} is independently a rigid linker aryl substituent;

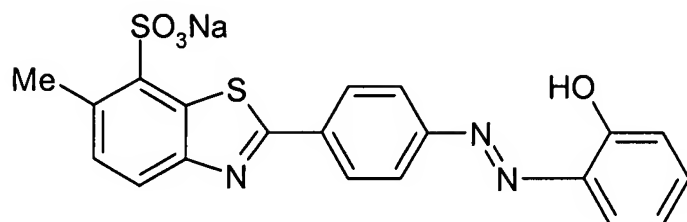
s is an integer from 0 to 4;

each R^A is independently an aryl substituent; and,

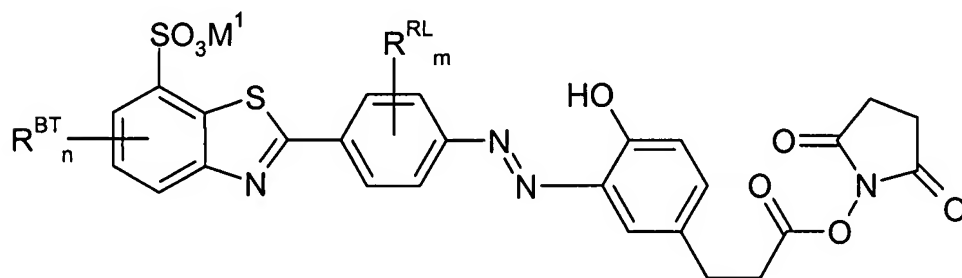
R^C , if present, is a reactive conjugating substituent, or

R^C is, or contains, a detectable label.

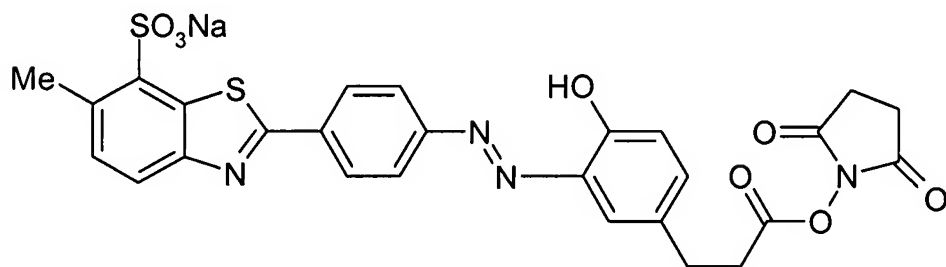
195. (Withdrawn). A method as claimed in claim 194 wherein the ligand has the formula:



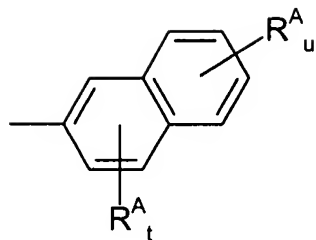
196. (Withdrawn). A method as claimed in claim 195 wherein the ligand has the formula:



197. (Withdrawn). A method as claimed in claim 196 wherein the ligand has the formula:



198. (Withdrawn). A method as claimed in claim 197 wherein Ar¹ is an aryl group having a naphthyl core, and has the formula:



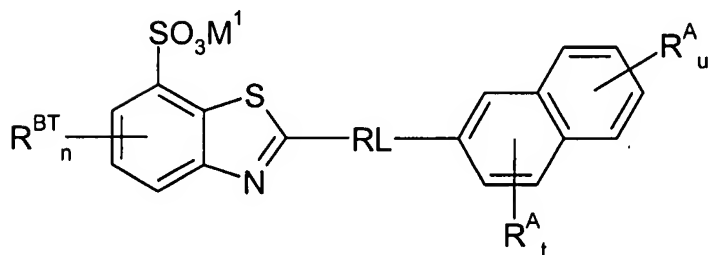
wherein

t is an integer from 0 to 3,

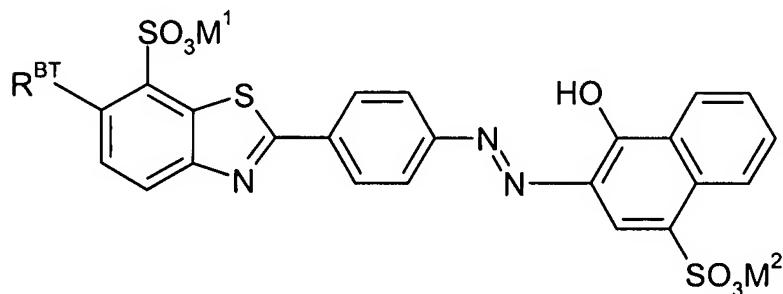
u is an integer from 0 to 4, and

each R^A is independently an aryl substituent,

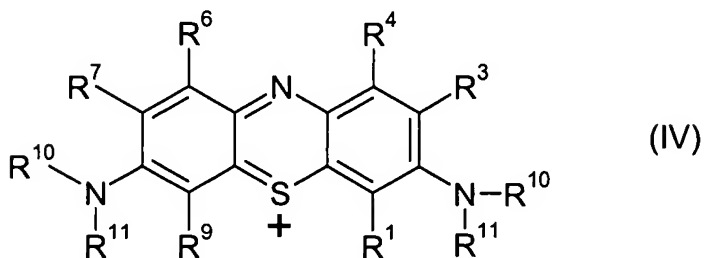
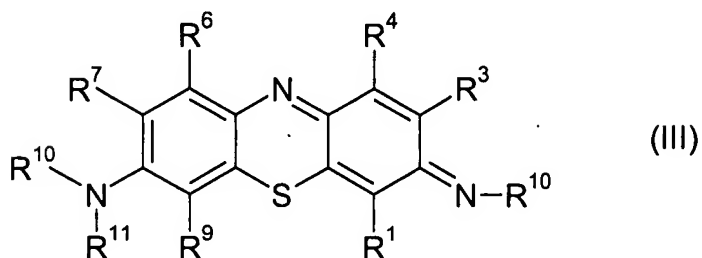
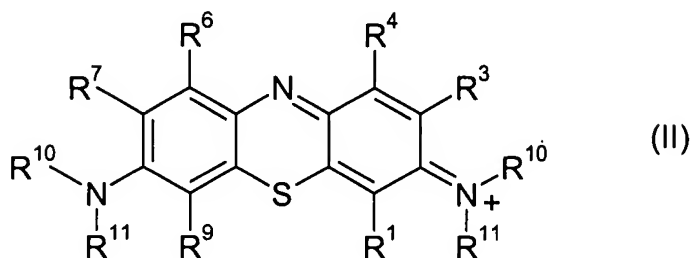
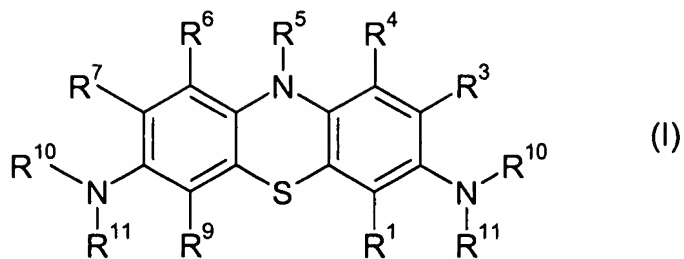
and the compound has the formula:



199. (Withdrawn). A method as claimed in claim 198 wherein the ligand has the formula:



200. (Previously Presented). A method as claimed in claim 175 wherein the ligand is a compound of one of the following formulae:



wherein:

each of R₁, R₃, R₄, R₆, R₇ and R₉ is independently hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R₅ is independently hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R₁₀ and R₁₁ are independently selected from hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

or a pharmaceutically acceptable salt thereof.

201. (Currently Amended). A method as claimed in claim 200 wherein the ligand is an acid addition salt formed between a the compound ~~described in said claims~~ and an acid which is an inorganic acid or an organic acid.

202. (Currently Amended). A method as claimed in claim 201 wherein the ligand is ~~shown in Figure 8b~~ **Tolonium Chloride, Thionine, Azure A, Azure B, 1,9-Dimethyl-Methylene Blue or Methylene Blue.**

203. (Previously Presented). A method as claimed in claim 200 wherein the ligand comprises a positron-emitting carbon.

204. (Currently Amended). A method as claimed in claim 175 which further comprises the step of ~~additionally~~ determining the presence and/or amount of a ligand bound to intracellular aggregated tau in a neocortical structure of the brain of the subject.

205. (Previously Presented). A method as claimed in claim 204 wherein the ligand used to bind to extracellular aggregated PHF tau in the medial temporal lobe and the ligand used to bind to intracellular aggregated PHF tau in the neocortical structure of the brain are labelled distinctively.

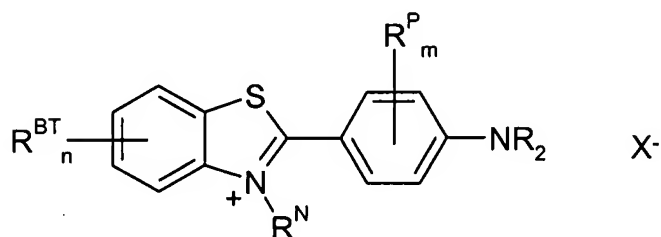
206. (Currently Amended). A method as claimed in claim 175 ~~wherein steps (i) and/or (ii) of the method are performed in conjunction with the further~~ **further comprising the** step of introducing into the subject a ~~further~~ blocking ligand which labels the competing **non-**

aggregated tau binding sites present in the ~~relevant region~~ medial temporal lobe and in a neocortical structure of the brain ~~preferentially to the ligand used to bind aggregated PHF tau.~~

207. (Currently amended). A method as claimed in claim 206 wherein the blocking ligand is selected from the ~~list~~ group consisting of:

[18F]FDDNP; and

a ~~benzthiazole~~ benzothiazole of the formula:



wherein:

n is an integer from 0 to 4;

each R^{BT} is independently a blocking ligand benzothiazole substituent which is independently C_{14} alkyl, $-SO_3H$, or $-SO_3M^3$, wherein M^3 is a cation,

m is an integer from 0 to 4;

each R^P is independently a ~~phenylene~~ phenyl substituent;

each R is independently -H or an amino substituent; and,

either:

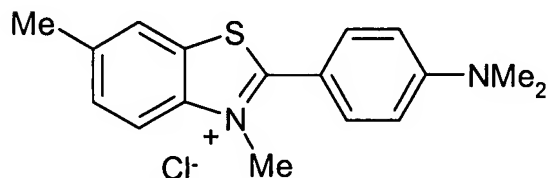
R^N and X^- are both absent and the associated (tertiary) nitrogen atom is neutral;

or:

R^N is a benzothiazolino substituent and the associated (quaternary) nitrogen atom bears a positive charge, and X^- is a counter ion.

208. (Previously Presented). A method as claimed in claim 207 wherein the blocking ligand is thioflavin-T.

209. (Currently amended). A method as claimed in claim 207 wherein the blocking ligand is a ~~benzthiazole~~ benzothiazole of the formula:



210. (Currently amended). A method as claimed in claim 207 wherein the blocking ligand is a ~~benzthiazole~~ benzothiazole of the formula:

